

Review Article

A rare case of Eosinophilic Pneumonia in an infant patient and review of the current English literature regarding this disease

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Abstract

We report a case of eosinophilic pneumonia (EP) in an infant patient. Such cases are rare and the purpose of this study is to combine this case and the english literature available in order to expand our knowledge regarding the therapeutic strategies for this disease. Currently we can define a specific therapeutic guideline for patients with EP. It is important to expand our knowledge and experience regarding this ailment. More studies are needed to better understand this rare disease, to more precisely define diagnostic and therapeutic strategies and to find out and asses new treatment methods.

Keywords: eosinophilic pneumonia (EP), types, rare, literature, treatment

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Abbreviations:

EP: Eosinophilic Pneumonia

AEP: Acute Eosinophilic Pneumonia

CEP: Chronic Eosinophilic Pneumonia

HES: Hypereosinophilic Syndrome

GPA: Granulomatosis with polyangiitis

WG: Wegener's Granulomatosis

BAL: Bronchoalveolar lavage

PEC: peripheral eosinophil count

IgE: Immunoglobulin E

CXR: Chest X-ray

CT: Computed tomography

RT: Radiation therapy

Th2: T helper 2

BALF: Bronchoalveolar lavage fluid

pNTM: pulmonary non-tuberculous mycobacteriosis

IL: Interleukin

anti-IL: anti-Interleukin

FEV1: forced expiratory volume in 1 second

PGD2: Prostaglandin D2

AQLQ: Asthma Quality of Life Questionnaire

ACQ: Asthma Control Questionnaire

T2: Type 2

Th2: T helper cell type 2

Introduction

Eosinophil

The purpose of this article is to further explore the topic of eosinophilic pneumonia (EP), as well as discuss current and future treatment options through a detailed literature review. Eosinophils, sometimes called eosinophils or, less commonly, acidophils, are a variety of white blood cells and one of the immune system components responsible for combating multicellular parasites and certain infections in vertebrates. (Cincinnati, available

<https://www.cincinnatichildrens.org>)

The eosinophil is in other words an end-stage granulocyte which is developed in the bone marrow, where it also differentiates from myeloid precursor cells (Lambrecht et. al., 2015; Metcalf D et. al., 1987, 1986; Yamaguchi et. al., Y 1988) and is known to circulate through the peripheral bloodstream and tissues. The eosinophil is composed of many granules containing enzymes and proteins (Stephanie S et. al., 2016; Adkinson NF et. al., 2014). Following activation by an immune stimulus, eosinophils degranulate to release an array of cytotoxic granule cationic proteins that are capable of inducing tissue damage and dysfunction. (Gleich GJ et. al., 1986) While normally appearing in smaller numbers in healthy people, eosinophils play a central role in inflammation and allergic process. (Waedlaw AJ et. al., 2000; Scott KA et. al., 2006; Adkinson NF et. al., 2009) They control mechanisms associated with allergy and asthma. The functional ambiguity of the Eosinophils belies a rich history of experimentation and evolving hypotheses that have slowly defined the importance of eosinophils as components of disease processes and the maintenance of homeostasis. (Lee J.J. et. al., 2012; Furuta GT. et. al.,

2014) An understanding of the historical context surrounding eosinophil biology is relevant as these changing perspectives developed from an underlying need to explain clinical observations and improve patient disease management. While they are released into the bloodstream as neutrophils are, eosinophils reside in tissue. (Rosenberg HF et. al., 2007) They are found in the medulla and the junction between the cortex and medulla of the thymus, and, in the lower gastro-intestinal tract, ovaries, uterus, spleen, and lymph nodes, but not in the lungs, skin, esophagus, or some other internal organs [vague] under normal conditions. The presence of eosinophils in these latter organs is associated with disease. For instance, patients with eosinophilic asthma have high levels of eosinophils that lead to inflammation and tissue damage, making it more difficult for patients to breathe. (Lambrecht BN et. al., 2015; Sanderson et. al., 1992) Some recent studies have suggested that peripheral blood eosinophil levels or the peripheral levels of unique eosinophil-specific markers correlate with disease severity (Furuta GT. et. al., 2014; Robinson D. S. et. al., 1995) the limited power of these studies and the publication of reports with conflicting conclusions (Stelmach P. et. al., 2004) have limited the usefulness of these systemic evaluations. Instead, the goals of assessment in these diseases have been site-specific sampling.

Pneumonia (Generally)

Pneumonia is an inflammatory condition of the lung affecting primarily the small air sacs known as alveoli. (Hui E. et. al., 2014; McLuckie et. al., 2009) Severity is variable. (Leach et. al., 2009) Pneumonia affects approximately 450 million people globally (7% of the population) and results in about 4 million deaths per

year. (Ashy B. et. al., 2007; Ruuskanen O. et. al., 2011).

Eosinophilic Pneumonia (EP)

Eosinophilic pneumonias (EPs) belong to the large group of interstitial lung diseases. (Lodha R. et. al., 2013; Giovannini L. et. al., 2016) They are characterized by a significant infiltration of the alveolar spaces and lung interstitium by eosinophils, with conservation of the lung structure. Eosinophilic pneumonia (EP), is also known as pulmonary infiltrates with eosinophilia (PIE syndrome), is a rare and heterogeneous syndrome that is classified according to inveteracy and etiology. This syndrome first described in 1989. (Nathan N. et. al., 2012; Bartal C. et. al., 2018) The currently used classification system of EP was described by Allen and Davis in 1994 (Allen JN. et. al., 1989) EP is infectious. It spreads through sneezes or coughs, but it spreads slowly. Eosinophilic pneumonia is divided into different categories depending upon whether a cause can be determined or not. Known causes include certain medications or environmental triggers, parasitic infections, and cancer. EP can also occur when the immune system attacks the lungs, a disease called eosinophilic granulomatosis with polyangiitis. When a cause cannot be found, the EP is labeled "idiopathic". Idiopathic EP can be divided into "acute eosinophilic pneumonia" (AEP) and "chronic eosinophilic pneumonia" (CEP) depending on the symptoms a person is experiencing. (Allen JN et. al., 1994) The following table represents the classification of the EPs. The various types of eosinophilic pneumonia have similar signs and symptoms. In particular acute eosinophilic pneumonia typically follows a rapid course. Chronic eosinophilic pneumonia usually follows slower course. The symptoms

accumulate over several months. Individuals with CEP are often misdiagnosed with asthma before CEP is finally recognized. When eosinophilic pneumonia is related to an illness such as cancer or parasitic infection, treatment of the underlying cause is effective in resolving the lung disease. When due to AEP or CEP, however, treatment with corticosteroids results in a rapid, dramatic resolution of symptoms over the course of one or two days. Either intravenous methylprednisolone or oral prednisone are most commonly used. In AEP, treatment is usually continued for a month after symptoms disappear and the x-ray returns to normal. In CEP, treatment is usually continued for three months after symptoms disappear and the x-ray returns to normal. In summary, eosinophils in the respiratory system can produce a wide array of symptoms, leading to many common as well as some more rare disease processes. While eosinophils can affect many different organ systems, eosinophil pathology in the respiratory system is a commonly encountered issue affecting both pediatric and adult populations. The involvement of eosinophils in pulmonary disease processes can affect the method of diagnosis and the selection of treatment modalities. By analyzing the complex interaction between the eosinophil and its environment, which includes signaling molecules and tissues, different therapies have been discovered and created in order to target disease processes at a cellular level. The topic of innovative treatments such as mepolizumab, benralizumab, lebrikizumab, dupilumab, reslizumab, and omalizumab will be explored in the following sections.

Table 1: Classification of eosinophilic pulmonary diseases

A) Idiopathic eosinophilic lung diseases	B) Secondary eosinophilic lung diseases
Löffler Syndrome (Simple Pulmonary Eosinophilia) Acute Eosinophilic Pneumonia (AEP) Chronic Eosinophilic Pneumonia (CEP) Hypereosinophilic Syndrome (HES)	1. Medication triggered Aminosalicylic acid Bicalutamide Non-Steroidal Anti-Inflammatory Imipramine Bleomycin Interleukin-2 and -3 Captopril Mecylamine Cocaine Methylphenidate Sodium Chromogluconate Minocycline Ethambutol Phenytoin Salts of gold Trazodone Heroin Trimipramine
	2. Parasitic causes Ascariasis Paragonimiasis Strongyloidiasis Tropical eosinophilia Ancylostomiasis Schistosomiasis
	3. Fungal etiology Allergic Bronchopulmonary Aspergillosis Coccidioidomycosis Trichosporonosis Invasive aspergillosis Other fungi
	4. Bacterial etiology
	5. Viral etiology
	6. Connective tissue diseases and vasculitis Granulomatosis with polyangiitis (GPA) or Wegener's Granulomatosis (WG) Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome) Rheumatoid arthritis Polyarteritis nodular
	7. Inhalation of toxic gases
	8. Other (unclassified) eosinophilic lung diseases Eosinophilic Gastroenteritis Vascularimmunoblastic Lymphadenopathy Reptile Bite Hystecytosis - X Inflammatory Bowel Disease Malignant Diseases Bone marrow transplantation of Idiopathic Pulmonary Fibrosis Asthma Eosinophilic Bronchitis

Case Presentation

4, 5-Month-Old female died during transport to the hospital and then the following results raised from the autopsy and autopsy histopathology.

Materials and Methods

Macroscopic findings: I received in a plastic container with formalin:

A. Brain tissue of 10 x 9 x 2 cm and weighing 89.7 g.

B. En bloc intestines with a total weight of 477.8 g, consisting of:

1. Tongue, trachea and aorta.

2. Heart of dimensions 5,5 x 4 x 2,5 cm and weighing 34,6 g.

3. Right lung with larger dimension more than 9 cm long and left lung with larger dimension of 8.5 cm.

4. Stomach, liver and spleen.

5. Right kidney with larger dimension of 5 cm and a left kidney with larger dimension of 4.8cm.

Results

Microscopic examination:

A. Brain tissue with localized destruction of the brain matter, edema, cells with eosinophilic cytoplasm and deep-chromatic nuclei, with the presence of inflammatory summations and varying degrees of congested vessels with localized overlapping wall.

B.

1. Tongue and trachea in places with mild inflammatory infiltrates, while six lymph nodes are recognized. Aorta in which within the lumen there are inflammatory effusion, fibrin, phagocytes and hemosiderin granules.

2. Myocardium with autolysis sites, localized medial edema, focal interstitial fibrosis mainly perivascular, areas in which the myocardial fibers exhibit cortical morphology and local disorder in terms of their layout. Also,

inflammatory cells, mainly eosinophils and lymphocytes, phagocytes, hemosiderin granules, are recognized, while inflammatory effusion with fibrin and hemosiderin granules, as well as thickened vessels, are locally detected intra-cardiac.

3. Pulmonary parenchyma in places with edema, with the presence of relatively sparse eosinophilic material in alveoli and bronchioles, areas with fibrous connective tissue in dense layout, whereas foci with condensing of the alveoli are found, areas with bronchial / bronchiolar / alveolar destruction are found to varying degrees in the fibrin reticulum bronchi, inflammatory effusion, relatively thick eosinophilic vitreous membranes, and concretion of cells and locally relative increase of mucus secreting cells. Inflammatory infiltrates, mainly eosinophilic cells and lymphocytes, abundant phagocytes, hemosiderin granules are also recognized, with the presence of multinucleated giant cells, impacted corpuscles, lymph nodes, and arterioles with overlapping wall.

4. Stomach in places with mild inflammatory infiltrates.

Liver with localized relatively distended sinusoids, autolysis sites and necrosis sites, mild inflammatory summations, phagocytes and hemosiderin granules. Spleen with locally distended pulp crossbeams, areas with fibrosis, multiple phagocytes and hemosiderin granules.

5. Renal parenchyma in which there are autolysis sites, inflammatory cells, phagocytes, hemosiderin granules and arterioles are sparsely scattered with overlapping wall are found to some extent congested.

Discussion

The types of Eosinophilic Pneumonia (EP) have been previously mentioned. The characteristics of AEP and CEP are going to be mentioned below. Acute

eosinophilic pneumonia (AEP) is notable for diffuse pulmonary infiltrates and elevated pulmonary eosinophils in the presence of high-grade fevers and may rapidly progress to acute respiratory failure. In addition to fever, nonproductive cough, shortness of breath, fatigue, myalgias, night sweats, and pleuritic chest pain may be present. (Pigakis K. et. al., 2008) Clinical exam findings include tachypnea, tachycardia, and crackles or rhonchi on lung auscultation. Radiographic findings on chest X-ray (CXR) include pulmonary edema, Kerley B lines, pleural effusions, and diffuse pulmonary infiltrates, which are more central and not characteristically seen in peripheral lung fields. Characteristic findings on computed tomography (CT) of the chest include diffuse interstitial and patchy alveolar infiltrates leading to a ground glass appearance. (Michael E. et. al., 2007) AEP affects males twice as often as females and can occur at any age, though the average age of onset is about 30 years. (Daimon T. et. al., 2008) Patients do not typically have a previous history of asthma. The etiology of the disease is unknown, but it is thought to be associated with environmental exposures. Bronchoalveolar lavage (BAL) is helpful for diagnosis, and identification of a concentration of greater than 25 % eosinophils is characteristic of the disorder. Interestingly, eosinophils are not elevated in the bloodstream on presentation of AEP. AEP is a diagnosis of exclusion, and other causes of acute respiratory failure such as infection or drugs must be ruled out. While a portion of affected patients may spontaneously recover, treatment with corticosteroids and respiratory support typically leads to improvement, usually without recurrence of disease. Abnormalities on imaging studies and pulmonary

function tests usually return to normal once the disease is resolved. (Jang Won Sohn et. al., 2013; Philit et. al., 2002; Rose et. al., 2013)

Acute eosinophilic pneumonia should be included in the differential diagnosis of pneumonia, especially in patients who have recently started smoking. A recent change in smoking habits is associated with acute eosinophilic pneumonia, as are other toxins. (Janz DR. et. al., 2009; D Caroline L H Brackel et. al., 2015; Seung Yong Park et. al., 2017) In particular, a significant number of drugs and toxins have been associated with eosinophilic pneumonia. Toxins suspected to cause eosinophilic pneumonia include cigarette smoke. (Lomon J et. al., 2006). The diagnosis is supported by a temporal relationship to a drug or toxin. The condition usually resolves with removal from the agent and recurs with rechallenge. Treatment involves discontinuation of the offending drug or toxin and treatment with corticosteroids in severe respiratory failure. (Takeuchi A. et. al., 2016) The cause of AEP is unknown, but it has been suggested that it may represent an acute hypersensitivity reaction due to unidentified antigens. Smoking is thought to be a risk factor for the development of AEP. (Uchiyama H. et. al., 2008; Bok GH, et. al., 2008; Nakajima M. et. al., 2002) AEP can develop soon after initiation of smoking as well as rechallenge with smoking after a period of abstinence. (Min Kyung Chung et. al., 2014) AEP has also been reported with secondhand smoke exposure. (Takeuchi A. et. al., 2016). Previous reports (Shiota Y. et. al., 2000; Shintani H. et. al., 2000; Watanabe K. et. al., 2002; Kitahara Y. et. al., 2003) suggest that AEP is related not only to the new onset of smoking, but also to resumption of smoking or the increase in the quantity of cigarette smoking.

The mechanism by which cigarette smoke induces AEP is not fully known. Cigarette smoke has been shown to be a strong inflammatory stimulus that recruits macrophages and neutrophils to lung tissue, and further induces pro-inflammatory cytokines and chemokines, such as interleukin-6, tumor necrosis factor, and interleukin-8. However, there is no concrete evidence that cigarette smoke itself directly induces eosinophilic inflammation in the lung. Recently, short-term cigarette smoke exposure has been shown to enhance pulmonary eosinophilic infiltration, as demonstrated by the marked increase in the levels of eotaxin in a mouse model of ovalbumin-induced allergic airway inflammation. (Nakajima M. et. al., 1997) Clinicians should maintain a high index of suspicion for AEP in any patient with a new smoking habit. This may be especially important in the military population, where the prevalence of tobacco use is higher than in the civilian sector. (Kuschner WG. et. al., 1996) Clinical outcomes of corticosteroid treatment in patients with AEP are good, and most AEP patients improve rapidly. There are no controlled clinical trials to determine the duration of corticosteroid therapy for AEP. Consequently, current practice derives from expert opinion (Jhun BW. et. al., 2014) without the assistance of clinical practice guidelines, which would help clinicians weigh the benefits relative to the potential harm of various durations of therapy. (Heffner JE. et. al., 2015) Tapering of corticosteroids has been evaluated in a previous study. It demonstrated non-inferiority of 2-week compared with a 4-week corticosteroid treatment. (Demirjian L. et. al., 2006; Kramarow EA et. al., 2012) However, in that study, the tapering of corticosteroid was not adjusted to disease severity. All AEP patients

received 2-week tapering. Only the mild cases underwent conservative treatment. We have no guidance to stratify disease severity of AEP, which may lead to overtreatment of mild cases. We have stratified AEP according to the presence of initial eosinophilia: AEP with initially normal PEC is considered a severe disease and AEP with initial eosinophilia is considered a milder disease. We developed a treatment protocol, with a rapid corticosteroid tapering strategy, in patients with initial eosinophilia. The most important finding in this study was that no treatment failure occurred in AEP patients with initial eosinophilia who underwent rapid corticosteroid tapering, strengthening the results, that an initially elevated PEC was associated with milder disease. (Kubo S. et. al., 2005; Jhun BW. et. al., 2015; Rhee CK. et. al., 2013) These results suggest that shorter treatment courses of corticosteroid may be an acceptable strategy in managing AEP with initial eosinophilia. Unfortunately, what logic suggests would represent conservative and therefore safe therapy—giving corticosteroids long enough to ensure full recovery and prevent a relapse—may actually cause harm if patients would have recovered sooner, but developed side effects from unnecessarily prolonged drug therapy. Of note, some patients with AEP recover spontaneously without corticosteroid treatment so it seems implausible that all patients who clinicians choose to treat will require a minimum of 2 weeks or more of drug therapy. In conclusion, the above mentioned data support as the best solution the individualization of therapy based on the severity of the initial disease and the response to corticosteroid therapy. Another study tried to evaluate the course of clinical stability in patients with acute

eosinophilic pneumonia (AEP) who did not receive corticosteroid treatment. Although the severity of AEP varies from mild dyspnea to life-threatening respiratory failure (Jantz MA. et. al., 1999; Guyatt G. et. al., 2006; Byung Woo et. al., 2015) AEP is characterized by a rapid response to corticosteroids. In addition, spontaneous recovery without any treatment has been reported, (Carrington CB et. al., 1969; Yunjie Ge. et. al., 2013; Hayakawa H. et. al., 1994; Umeki S. et. al., 1992) even in patients with severe respiratory failure. (Pope-Harman A. et. al., 1996) In that study, AEP-associated symptoms and signs were spontaneously resolved within a median of 9 days. In addition, the majority of pulmonary infiltrates on chest radiographs also completely disappeared within 14 days after diagnosis. However, the peripheral eosinophil counts and the frequency of peripheral eosinophilia increased up to 10 days and then decreased during the follow-up period. All patients in this study population experienced peripheral eosinophilia ($500/\text{L}$) during hospitalization. However, these findings might be limited to relatively mild cases of AEP. These data may assist physicians in determining the optimal timing for initiation of corticosteroids when clinical abnormalities are not resolved during a follow-up period without corticosteroid treatment. However, the clinical situations in which spontaneous resolution can be predicted at the time of diagnosis and which conservative treatments without corticosteroids are sufficient for patients with AEP remain unknown. Although spontaneous improvements have even been reported progression to life-threatening hypoxemia or death from AEP can occur. (Uchiyama H. et. al., 2008) Therefore, further studies of clinical characteristics or parameters that more

precisely reflect the grade of the inflammatory process in AEP are required.

First described by Charles B. Carrington in the *New England Journal of Medicine* in 1969, chronic eosinophilic pneumonia (CEP) is a rare disorder, with many reports of this illness being limited to case studies. (Kawayama T. et. al., 2002; Lim SY. et. al., 2012) Though the exact etiology is unknown, the disease is often associated with a high eosinophilic presence in lung tissue. (Philit F. et. al., 2002; Shorr AF et. al., 2004) In contrast with AEP, the majority of patients with CEP have a previous history of asthma. The presentation of CEP is variable, but tends to be a subacute or chronic course of mild symptoms. Pulmonary and hematologic eosinophilia are typical, and imaging studies reveal peripheral pulmonary infiltrates. Most patients are diagnosed in their third or fourth decade of life, though CEP may present in any age group. CEP has a predilection for women with a ratio of 2:1 female to male diagnoses. The disease is more often seen in nonsmokers. Symptoms include cough, progressive dyspnea, chest pain, weight loss, night sweats, and fever. Patients with CEP, unlike patients with AEP, are likely to present with a slightly elevated temperature that is less than 38°C . Diagnostic criteria for CEP includes pulmonary symptoms of at least 2-week duration, eosinophilia in the lung or blood- stream, peripheral pulmonary infiltrates on imaging studies, and exclusion of other common eosinophilic lung diseases. (Cottin V. et. al., 2005) BAL eosinophil count of $>40\%$ and blood AEC of $>1000\text{ cells}/\mu\text{L}$ are typical. Blood and alveoli eosinophils may be elevated to over $5000\text{ cells}/\mu\text{L}$ and 60% , respectively. Laboratory findings in addition to leukocytosis and peripheral

eosinophilia include elevated serum IgE and markers of inflammation, such as erythrocyte sedimentation rate and C-reactive protein. (Philit F. et. al., 2002; Shorr AF et. al., 2004) In contrast to AEP, CEP does not progress to acute respiratory failure. Characteristic imaging findings in CEP include dense, multifocal consolidations in a bilateral and peripheral distribution on CXR. Findings on chest CT include bilateral consolidations and a ground-glass appearance. (Cottin V. et. al., 2005; Philit F. et. al., 2002) Treatment regimens include systemic corticosteroid therapy, which typically produces a favorable response and rapid improvement. The course may be relapsing and remitting in some patients, with up to 50 % of patients experiencing a relapse of symptoms one or more times after treatment. Management also involves good control of underlying asthma, and some patients may require long-term oral corticosteroid treatment to keep both asthma and CEP well controlled. (Stephanie S. et. al., 2016; Philit F. et. al., 2002)

A previous study describes the occurrence of chronic eosinophilic pneumonia following RT after surgery for breast cancer in five female patients, with a mean age of 68 yrs (range 49–77) suggesting that radiation to the lung may promote the development of chronic eosinophilic pneumonia similar to that described for organising pneumonia. (Akuhota P. et. al., 2012; Cottin V. et. al., 2012) All five patients had been treated by surgery for localized breast carcinoma. In all patients, breast surgery was followed by RT. Priming of alveolitis by radiation therapy to the breast might promote chronic eosinophilic pneumonia, which depends on genetic or acquired characteristics of patients and/or further stimulation that may

trigger a T-helper cell type 2 form of lymphocyte response, especially in patients with asthma or other atopic manifestations. All patients had a history of asthma and/or allergy. A strong association between idiopathic chronic eosinophilic pneumonia and asthma is now well established. (Crestani B. et. al., 1998) At the onset of eosinophilic pneumonia, all patients were symptomatic. Chest radiograph showed pulmonary infiltrates, unilateral, which is a feature that is unusual in idiopathic chronic eosinophilic pneumonias, (Cottin V. et. al., 2004) further suggesting that RT may have contributed to the development of this syndrome, and limited to the irradiated lung in three patients, and bilateral in two. Pulmonary opacities were migratory in one patient. All patients had blood eosinophilia $>1.0 \times 10^9 \text{ L}^{-1}$ and/or eosinophilia $>40\%$ at bronchoalveolar lavage differential cell count. The median time interval between the end of radiation therapy and the onset of eosinophilic pneumonia was 3.5 months (range 1–10). The time course of the chronic eosinophilic pneumonia was compatible with a role of RT, since previous studies have demonstrated that radiation-induced organising pneumonia may develop within a year after the completion of RT. (Akuhota P. et. al., 2012; Marchand E. et. al., 1998) All patients rapidly improved with oral corticosteroids without sequelae. Relapse occurred in two patients after treatment withdrawal. The eosinophilic pneumonia again completely resolved after corticosteroids were resumed. The authors hypothesize that chronic eosinophilic pneumonia may be facilitated by lung irradiation. Indeed, a slightly elevated number of eosinophils in bronchoalveolar lavage cell count have been reported in patients receiving RT following breast

cancer surgery. (Marchand E. et. al., 2003) RT induces a diffuse bilateral and persistent lymphocytic alveolitis. (Bayle JY et. al., 1995) The development of chronic eosinophilic pneumonia may then be triggered by other factors such as drugs, *Aspergillus* infection, and environmental exposures. The authors speculate that antigenic stimulation may trigger a Th2-type of lymphocyte response when occurring in the weeks following lymphocyte priming by RT, thus leading to the occurrence of chronic eosinophilic pneumonia. The Th2- type immunological response may also be further facilitated by individual susceptibility and genetic factors, which were indeed suggested by a history of asthma or allergy in patients in that study. In conclusion, these observations suggest that chronic eosinophilic pneumonia may be included in the spectrum of potential pulmonary changes secondary to radiation therapy to the chest. Although a causal relationship between radiation therapy and chronic eosinophilic pneumonia cannot be definitively established from that descriptive study, the authors hypothesize that priming of alveolitis by radiation therapy to the breast may result in either chronic eosinophilic pneumonia or organising pneumonia, depending on the genetic or acquired characteristics of patients and/or further triggering factors.

Our knowledge about the predictive factors of relapse of CEP is limited. One report has assessed the predictive factors of CEP relapse, and to date, it is not known which factors are predictive of relapse of CEP. (Bjerner L. et. al., 1990; Roberts CM. et. al., 1993). The cessation of smoking stops the relapse of CEP and it is advised in CEP patients. Other factors on presentation, including age, sex, history of dust exposure, underlying

disorders (asthma and allergic disorders), respiratory failure, peripheral eosinophilia, serum IgE level ($>1,000$ IU/mL), rate of eosinophils in the BALF, CD4/8 ratio in the BALF, and inhaled steroid therapy, were not significant predictive factors by univariate analysis. Although corticosteroid therapy remains a mainstay of CEP treatment, prolonged corticosteroid administration may induce metabolic and infectious complications. Future studies are needed to clarify the effects of prolonged corticosteroid therapy on the cardio-vascular system in CEP patients. One additional patient of the study developed pNTM, for which corticosteroid is a risk factor. The limited number of patients with pNTM did not allow us to assess whether the incidence of pNTM was higher in our CEP patients than that already reported. (Takashi Ishiguro et. al., 2016) Additional treatment options are expected in the future. A history of smoking was a predictive factor for relapse of CEP at the time of initial diagnosis. One possible explanation of the results is the contribution of smoking to the development or maintenance of eosinophilic infiltration in the lung. (Oyama Y. et. al., 2015) Although no reports have suggested an association between smoking and CEP, there is significant overlap between CEP and acute EP, for which a strong association exists with cigarette smoking. (Bjerner L. et. al., 1990; Sakatani M. et. al., 2005) Smoking causes cellular and molecular changes that can lead to inflammation. In response to smoking, inflammatory signaling is altered by airway epithelial cells and macrophages, which, according to the signaling pathway used, results in an increase of lymphocytes, eosinophils, neutrophils, and mast cells in the lungs. In response to the exposure to smoking, a number

of proteins are upregulated and secreted, many of which have immunomodulatory activities that contribute to the pathogenesis of disease. (Bjermer L. et. al., 1990; Botelho FM. et. al., 2011) The inflammatory process induced by smoking is halted by its cessation, and all of our patients stopped smoking after the diagnosis of CEP, which may have helped to prevent the relapse of CEP. Large, prospective studies will be needed in the future to clarify this matter. CEP frequently relapses, and a history of smoking in patients at the time of the initial diagnosis of CEP was found to be a negative predictive factor for relapse of CEP. There may be some population of CEP patients in whom smoking contributes to the development or maintenance of CEP. The relapse of CEP may be halted by smoking cessation, which is strongly suggested in CEP patients.

In a group study, patients with CEP received oral prednisolone for either 3 months (3-month group) or 6 months (6-month group), followed by 2 years observation. All patients were treated with an initial dose of prednisolone of 0.5 mg/kg perday, which was then tapered and discontinued at either 3 or 6 months. In the final analysis, there were 23 patients in the 3-month group and 21 patients in the 6-month group. All patients showed a good response to prednisolone treatment. There were 12 (52.1%) relapses in the 3-month group and 13 (61.9%) relapses in the 6-month group. No significant difference was found in the cumulative rate of relapse. All relapse cases showed improvement upon resumption of prednisolone treatment. No difference was observed in the rate of relapse between the 3- and 6-month prednisolone treatment groups for patients with CEP. In the study the efficacy and safety of 3- and 6-month prednisolone treatment for patients with CEP was

compared. Collectively, these data demonstrate that the efficacy of 3 months of prednisolone treatment may be equivalent to that of 6 months of treatment for patients with CEP, particularly in relation to relapse. Given the risks of long-term prednisolone treatment, 3 months of treatment may represent a more suitable and even feasible therapeutic option for patients with CEP (Akuhota P. et. al., 2012).

Drug-induced EP is a rare condition. In total, only 228 cases were reported between 1990 and March of 2017. Ultimately, 196 full-text case reports met the criteria to be included in the following analysis. Many medications were implicated in drug-induced EP and the most commonly cited drugs were daptomycin, mesalamine, sulfasalazine, and minocycline. Almost every family of medication was found to be implicated. Moreover, A higher prevalence among a few pharmacological families such as antibiotics, (Nathan N. et. al., 2012; Crotty Alexander et. al., 2015) nonsteroidal anti-inflammatory drugs (Hirai J. et. al., 2017; Klerkx S. et. al., 2009) and antiepileptic drugs was found, (Anan E. et. al., 2009) which suggests the possibility that there is a connection between the pathogenesis of EP and the mechanism of action of those commonly used medications. (Nathan N. et. al., 2012; Uchiyama H. et. al., 2008; Klerkx S. et. al., 2009). Regardless of age or sex, drug-induced EP should be suspected in any patient who has recently started taking a new medication and presents with new-onset dyspnea, bilateral infiltrates on chest radiograph, and peripheral blood eosinophilia with a negative eosinophilia work-up.

Given the fact that our patient was an infant, Eosinophilic pneumonias in children should be explored. Eosinophilic pneumonia is

not common in the pediatric population. The mean age is typically in the late 20s. (Sauvaget E. et. al., 2010) Only three pediatric cases of acute idiopathic EPs have been described in France in the last decade. (Kim JH. et. al., 2013) Despite their rarity, the etiological approach to EP has to be well-defined, as some causes can be rapidly life-threatening (Rizos E. et. al., 2013) without initiation of the proper treatment. An extensive description of adult EPs has been proposed, (GiovanniniChami L. et. al., 2014; Lodha R. et. al., 2013) but specific descriptions of childhood EPs in both developing and developed countries and their etiological approach have not been reviewed to date.

The etiological approach has to be well documented in order to diagnose potentially life-threatening conditions. Asthma is a heterogeneous disease, which is characterized by chronic airway inflammation, episodic respiratory symptoms, and associated with variable expiratory airflow limitation, and can be divided into different clinical phenotypes. (Lambrecht BN et. al., 2015; Fa-Ping Wang et. al., 2018) Based on the sputum and peripheral blood cellular profiles, asthma can be classified into eosinophilic or non-eosinophilic. (R. H. Green et. al., 2002; Imran Iftikhar et. al., 2018; McGrath KW. et. al., 2012) Since eosinophilia can be seen across multiple clusters of asthma and disease severity, focus is shifting toward identifying different mechanisms that cause eosinophilia. (Pang PH. et. al., 2017; Jatakanon A. et. al., 2000). Among these are elevated interleukin (IL)-4 and IL-13 expression in early-onset atopic asthma and predominant IL-5 expression in later-onset, or less-atopic asthma. Understanding the heterogeneity of the airway

inflammation in severe asthma is of particular importance to predict future risk of exacerbations and response to therapy. Asthma exacerbations are associated with substantial morbidity and mortality. (Carr TF. et. al., 2018). Decreasing the asthma exacerbations rate is a key goal of asthma management. The presence of eosinophilic airway inflammation is associated with poorer asthma control and increased risk of exacerbations, and is a good predictor of a favorable response to corticosteroids. Quite a few outcomes in asthma have underlying refractory asthma, in whom standard therapies are ineffective. (Gibson PG, 2009) Several new 'biologics' have emerged as promising personalized medicines specifically in the treatment of severe eosinophilic asthma. 'Biologics' are drugs such as omalizumab, Anti-interleukin-5 monoclonal antibodies (mepolizumab, reslizumab, benralizumab) and so on, which are produced by living cells through biological processes, and mimic natural biological substances such as antibodies targeting specific inflammatory pathways. The effects of the cytokines in the eosinophils are a matter of current research. Eosinophil recruitment and production is due to Th2 lymphocyte stimulation, with the help of cytokines including IL-3, IL-4, IL-5, IL-13^[14]. According to Stone et al., these interleukins function in different ways. IL-4 and IL-13 stimulate immunoglobulin (Ig) E production and promote eosinophil recruitment by increasing expression of eotaxin (CCL11 and CCL26) and endothelial cell vascular cell adhesion molecule 1 (VCAM1). IL-5 mediates enhanced eosinophil production, eosinophil egress from the bone marrow, and eosinophil activation and survival. This cytokine is specific to eosinophil development but is not responsible for fostering eosinophil

infiltration of specific tissues. Most eosinophils that enter circulation from the bone marrow traffic to specific tissues and never return to circulate in the peripheral bloodstream. The process of eosinophils trafficking to tissues is thought to be overseen by T cells responding to antigen-presenting cells. However, when inflammation regulated by Th2 cells is present, eosinophils will home to other organs including the lungs and skin. Once trafficking to tissues is complete, the eosinophil attaches to extracellular matrix protein, fibronectin, which binds the eosinophil to specific tissues. Subsequently, the eosinophil receives a signal to degranulate and releases the preformed components of its granules, such as proteins as well as cytokines and chemokines. (Masoli M. et. al., 2004; Chung KF. et. al., 2014) In another study the authors speculate that IL-5 is essential for eosinophilic migration to the lung.

Most diseases require corticosteroid therapy, both systemic and those targeted at specific tissues, with inconsistent results and cure rates. New therapies to target the inflammatory cascade remain at the forefront of research in eosinophilic disease processes. However, despite the use of high dosages of these drugs, even when associated with recurrent and long-lasting courses of systemic corticosteroids; some patients with refractory eosinophilic asthma do not achieve an adequate control of their disease. Such subjects can thus significantly benefit from add-on biological therapies.

The first monoclonal antibody for asthma was omalizumab, a humanized monoclonal antibody against IgE used since 2003 in adults, adolescents and children over 6 years of age with moderate to severe persistent allergic asthma inadequately controlled with standard therapy. It improved asthma

symptoms and health-related quality of life. It also reduced exacerbations and daily inhaled corticosteroid dose. (Kumar R. et. al., 2014). Response to omalizumab was better in asthmatics with increased biomarkers of T2 immunity and eosinophilic inflammation.

Anti-interleukin-5 (IL-5) monoclonal antibodies are the second class of biological therapy for severe eosinophilic asthma. IL-5 cytokine plays an important role in the maturation and activation of eosinophils as mentioned before. Mepolizumab is a humanized monoclonal antibody that binds to IL-5, preventing it from binding to IL-5 receptors. The first large phase IIb/III trial (DREAM study) showed that mepolizumab at a range of doses significantly reduced severe exacerbation rate in subjects with recurrent exacerbations and evidence of eosinophilic inflammation. (Adkinson NF et. al., 2009) Mepolizumab has also been shown to have steroid-sparing effects by significantly reducing daily systemic corticosteroid use compared to placebo, while maintaining its exacerbation reduction effect. (Stone KD et. al., 2010) The efficacy of mepolizumab appeared to be more pronounced in subjects with higher baseline blood eosinophil levels and more frequent exacerbations, with no benefit in exacerbation reduction in those with a blood eosinophil count <150 cells/L. On the strength of these positive trial results, it has since been licensed for use in severe eosinophilic asthma. According to another study, mepolizumab significantly reduces the risk of exacerbations requiring hospitalization or a visit to the emergency room. Last but not least, previous studies have shown that mepolizumab is associated with a clinically acceptable safety profile

across a number of conditions. (Normansell R. et. al., 2014; I.D. Pavord et. al., 2012; Bel E. H. et. al., 2014; Steven W. Yancey et. al., 2017; Haldar P. et. al., 2009) Mepolizumab therefore represents an important treatment option for patients with severe eosinophilic asthma, and addresses a patient population that currently has a high unmet need and limited treatment options. Reslizumab, another monoclonal antibody targeting IL-5, was also recently licensed for use in severe eosinophilic (≥ 400 blood eosinophils/L) asthma following phase III trials demonstrating significant improvement in forced expiratory volume in 1 second (FEV1), asthma control scores, asthma-related quality of life and frequency of asthma exacerbations. (Ortega H. G. et. al., 2014) However, when used across a broad range of blood eosinophil counts, reslizumab had no effect on lung function and asthma control. (Flood-Page P. et. al., 2007). Benralizumab differs from mepolizumab and reslizumab as it acts on the alpha chain of the IL-5 receptor causing eosinophil apoptosis. Two recent phase III trials in subjects with inadequately controlled asthma, frequent exacerbations and elevated blood eosinophil count showed significant reduction of annual asthma exacerbation rate compared to placebo (Roufosse F. E. et. al., 2013; Straumann A. et. al., 2010). Inhibiting other T2-cytokines such as IL-13 neutralization (Lebrikizumab and Tralokinumab) or the alpha chain of the IL-4 receptor which attenuates both IL-4 and IL-13 signaling (Dupilumab) are attractive targets. None of these strategies have demonstrated an effect on reducing eosinophilic inflammation, but benefits for these approaches are greater in those with upregulated T2-immunity and eosinophilic inflammation. Recent

phase III studies for Lebrikizumab failed to demonstrate consistent benefit for reduction in asthma exacerbations. Findings from a phase IIb study of Dupilumab were more encouraging, showing reductions in exacerbation frequency and improvements in symptoms in all comers with greatest response in those with eosinophilic inflammation. (M. Castro et. al., 2015; L. Bjermer et. al., 2016)

In addition to biological therapy, small molecule inhibitors have shown promising results in severe asthma. Prostaglandin D₂ (PGD₂) is a prostanoid mainly produced by mast cells, which binds and activates G protein-coupled receptors.

Many studies have tried to compare the efficacy of Anti IL-4, IL-5 and IL-13 Drugs for treatment of eosinophilic asthma. A network meta-analysis has shown that all treatments were comparable in terms of magnitude of improvement in FEV1 (except for tralokinumab) and AQLQ (except for tralokinumab and lebrikizumab). However, in the analysis of ACQ scores, mepolizumab had the greatest effect in terms of magnitude of improvement. Additionally, only dupilumab and reslizumab were associated with significantly less asthma exacerbations on treatment compared to others. In terms of comparison in this network meta-analysis, mepolizumab as a drug is at a disadvantage, primarily because the drug was not included in the sub-group analyses. Even otherwise, controversy exists over the apparent superiority of the newer drugs (such as benralizumab) over mepolizumab. Perhaps future trials on mepolizumab could compare the drug with other drugs by classifying based on biomarkers (Corren J. et. al., 2016; Bleecker E. R. et. al., 2016).

Table 2: Comparing acute and chronic eosinophilic pneumonia

	AEP	CEP
Etiology	Unknown, though associated with environmental exposures	Unknown, though associated with environmental exposures
Presentation	Acute symptoms which progress rapidly	Subacute, milder symptoms
Sex	Male predominance 2:1	Female predominance 2:1
Risk	Higher incidence in smokers	Higher incidence in nonsmokers
Labs	Normal eosinophil count to mild/moderate peripheral eosinophilia	Leukocytosis, peripheral eosinophilia (absolute eosinophil count >1000 cells/ μ L)
BAL	>25 % eosinophils	>40 % eosinophils
Imaging	Diffuse hazy infiltrates on chest imaging	Bilateral, dense multifocal consolidation on chest imaging
Course	Rapid progression to acute respiratory failure	Indolent course which may be relapsing and remitting, without respiratory failure
Atopy	Asthma does not predispose individual	Asthma predisposes individual
Management	Systemic corticosteroids	Systemic corticosteroids

The advent of a range of antibodies targeting different mechanisms in asthma should enable progress toward the goal of personalized medicine, in which existing biomarkers aid clinicians in matching each biologic therapy to the patient population most likely to benefit from that treatment. Future directions for research should include discovery of new biomarkers, exploration of combination therapies that target multiple pathways, and recognition of the disease underlying pathologies in additional patient subpopulations that might benefit from novel treatments (N. A. Hanania et. al., 2016; S. Wenzel et. al., 2016; J. Nixon et. al., 2017).

Conclusion

As mentioned above Eosinophilic Pneumonia (EP) is a really complex and serious disease and the current treatment methods are not adequate

sufficient and effective enough. Thus, the armamentarium for the treatment of severe eosinophilic pneumonia (EP) needs to be expanded. Future research is needed to give further insight into which patients are most likely to have the greatest response to which treatment, and to better define both response and failure to respond to these new therapies. This might require head-to-head pragmatic real life trials of licensed therapies. In conclusion, I am certain that with its overarching reach and relevancy too many patient populations, eosinophilic pneumonia (EP) will remain an important topic for many years to come.

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